Induction of Spindle Multipolarity by Centrosomal Cluster Inhibition

Cellular Oncology 30 (2008) 505–506
DOI 10.3233/CLO-2008-0450
IOS Press

Letter to the Editor

Induction of spindle multipolarity by centrosomal cluster inhibition *

Sir,

The centrosome is a small organelle which consists of two centrioles and a pericentriolar matrix [1]. It functions as the microtubule-organizing center of eukaryotic cells and plays a central role for the formation of the mitotic spindle. Supernumerary centrosomes have been described in almost all human malignancies, including brain, breast, colon, lung, pancreas, and prostate cancers as well as in leukemias and lymphomas [2–4]. Furthermore, a striking correlation between centrosome aberrations and chromosomal instability as well as clinical aggressiveness has been described for many tumor entities. Cells with supernumerary centrosomes usually form multipolar spindles which lead to aberrant mitoses and consequently to chromosome miss-segregation. To regain secondary karyotype stability after clonal selection, tumor cells coalesce their extra centrosomes by a poorly defined mechanism into two spindle poles in order to divide properly and thus to survive [5]. Here, we describe a screening procedure for the identification of both small molecules and siRNAs that inhibit centrosomal clustering and thus force tumor cells with supernumerary centrosomes to undergo multipolar mitoses and consequently apoptosis. For this purpose, squamous cell carcinoma cells which harbour extra copies of centrosomes (SCC114) and nevertheless divide in a strictly bipolar fashion [5] are used as a model system and treated with either small molecules or a whole genome siRNA library to investigate if they have an effect on spindle polarity. Analysis is performed by high-throughput microscopy, using a SCC114 clone that stably expresses GFP-α-tubulin. Using a genome-wide siRNA library resulted in the identification of $\sim$150 proteins involved in the clustering of supernumerary centrosomes into a bipolar mitotic spindle. Screening of a small molecule library led to the identification of several substances which are currently characterized in more detail. One of these substances is the well-known antifungal drug griseofulvin, which led to an increased frequency of multipolar mitoses, mitotic arrest and apoptosis in several different tumor cell lines whereas normal fibroblasts and keratinocytes were not affected [6]. In addition, a griseofulvin derivative inhibited *in vivo* tumor growth in a murine xenograft model of human colon cancer. The identification of proteins that are components of the centrosomal clustering machinery in tumor cells will help to clarify the mechanisms of how tumor cells coalesce supernumerary centrosomes into bipolar spindles. Furthermore, this knowledge will enable us to determine specific targets for anti-cancer therapy and thus for drug development.

Alwin Krämer[a,**], Marc S. Raab[b] and Blanka Rebacz[a]

[a]*Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center and Department of Internal Medicine, University of Heidelberg, Heidelberg, Germany*

[b]*Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*

*This work was presented at the 2nd Conference on Aneuploidy and Cancer, Oakland, January 31–February 3, 2008.

**Corresponding author: Alwin Krämer, Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center and Department of Internal Medicine, University of Heidelberg, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany. Tel.: +49 6221 421440; Fax: +49 6221 421444; E-mail: a.kraemer@dkfz.de.

References

[1] M. Bornens, Centrosome composition and microtubule anchoring mechanisms, *Curr. Opin. Cell Biol.* **14** (2002), 25–34.

[2] E.A. Nigg, Centrosome aberrations: cause or consequence of cancer progression?, *Nat. Rev. Cancer* **2** (2002), 815–825.

[3] K. Neben, C. Giesecke, S. Schweizer, A.D. Ho and A. Krämer, Centrosome aberrations in acute myeloid leukemia are correlated with cytogenetic risk profile, *Blood* **101** (2003), 289–291.

[4] A. Krämer, S. Schweizer, K. Neben, P. Lichter, U. Krause, C. Giesecke, J. Kalla, H.K. Müller-Hermelink, A.D. Ho and G. Ott, Centrosome aberrations as a possible mechanism for chromosomal instability in non-Hodgkin lymphomas, *Leukemia* **17** (2003), 2207–2013.

[5] N.J. Quintyne, J.E. Reing, D.R. Hoffelder, S.M. Gollin and W.S. Saunders, Spindle multipolarity is prevented by centrosomal clustering, *Science* **307** (2005), 127–129.

[6] B. Rebacz, T.O. Larsen, M. Clausen, M. Ronnest, H. Löffler, A.D. Ho and A. Krämer, Identification of griseofulvin as an inhibitor of centrosomal clustering in a phenotype-based screen, *Cancer Res.* **67** (2007), 6342–6350.